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RAWLINGS, STEPHEN L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/649,591	MARKOWITZ, SANFORD D.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75,84-91,93-102,104-106,123 and 124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75,84-91,93-102,104-106,123 and 124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 21, 2007, has been entered.

1. The amendment filed August 21, 2007, is acknowledged and has been entered. Claims 75, 93, 98, and 99 have been amended.

2. The amendment filed May 22, 2007, has been entered. Claim 125 has been cancelled. Claims 75 and 97 have been amended.

3. The amendment filed February 16, 2007, has been entered. Claim 103 has been canceled. Claims 87, 90, and 98-100 have been amended. Claim 125 has been added.

4. Claims 75, 84-91, 93-102, 104-106, 123, and 124 are pending in the application and are currently under prosecution.

Election/Restriction

5. In view of the decision on petition filed May 25, 2007, which was entered June 26, 2007, the requirement to restrict and elect a single species of the invention of Group I set forth in section 7, beginning at page 6 of the Office action mailed may 3, 2006, has been withdrawn. Accordingly, the claims are presently directed to a method for determining whether a subject is likely to have a colon neoplasm, said method comprising detecting in a biological sample obtained from the subject one or more

secreted polypeptides selected from the group consisting of: (a) a polypeptide produced by the expression of a nucleic acid having the nucleotide sequence of SEQ ID NO: 5; and (b) a polypeptide having the amino acid sequence of SEQ ID NO: 3, where the presence of said one or more secreted polypeptides indicates the subject is likely to have the neoplasm.

Response to Amendments

6. The amendments filed on February 16, 2007, and May 22, 2007, are considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution[1], rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised of following deficiencies:

The amendment filed February 16, 2007, is non-compliant because claim 99, for example, is not marked to show each and every change that has been made to the claim, relative to the prior version of the claim presented by the amendment filed November 6, 2006.

Similarly, the later filed amendment of May 22, 2007, is also not compliant for at least this same reason, regardless of whether the version of the claims presented by the amendment filed February 16, 2007, or the version presented by the earlier amendment of November 6, 2006, is regarded as the prior version.

In addition, the amendment filed February 16, 2007, is not compliant because the status identifier in parentheses of claim 99, for example, is improper; because the claim is amended, it is to be identified using the status identifier "Currently Amended", as opposed to "Previously Presented".

Despite the improprieties of these amendments, the set of claims submitted as part of the amendment filed August 21, 2007, has been used for the purpose of examination.

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[1] See M.P.E.P. § 714.03.

Priority

7. As noted in the preceding Office action mailed December 19, 2006, Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the U.S. Patent Application No. 10/274,591, filed October 18, 2002, which claims benefit of U.S. Patent Application No. 10/299,345, filed August 26, 2002, is acknowledged.

However, none of claims 75, 84-91, 93-102, 104-106, 123, and 124 properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

Again, to receive benefit of the earlier filing date under 35 USC § 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, as explained in the preceding Office action, claims 86 and 87 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed because the prior filed applications do not describe the practice of the claimed invention using a biological sample derived from the inner wall and/or lumen of the intestinal tract, such as a stool sample removed from within the colon.

Applicant's request for reconsideration of this issue with regard to claims 86 and 87 is noted. Beginning at page 10 of the amendment filed August 21, 2007, Applicant has argued claims 86 and 87 should benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed because both Application No. 10/274,177 and Application No. 10/229,345 describe detecting markers in stool samples.

Applicant's arguments have been carefully considered but not found entirely persuasive for the following reasons:

With regard to claim 86, although Application No. 10/274,177, for example, describes detecting whether a subject to likely to have a colon neoplasia by a process

comprising obtaining a stool sample from said subject and detecting the presence or absence of a polypeptide selected from the group consisting of ColoUp 1 polypeptide or ColoUp2 polypeptide, wherein the presence of said polypeptide is indicative of colon neoplasia (see, e.g., original claim 17), claim 86 of the present application is directed to a biological sample that "is derived from the inner wall and/or lumen of the intestinal tract". Though according to claim 87 the biological sample of claim 86 is a stool sample, claim 86 is not so limited. Neither of the prior filed applications describe the practice of the claimed invention using a biological sample derived from the inner wall and/or lumen of the intestinal tract, rather it appears the disclosures merely include a description of a biological sample that is a stool sample; accordingly, the Examiner disagrees with Applicant's assertion claims 86 should properly benefit from the filing dates of the prior filed applications. It is however agreed that were the rejections of claim 87 under 35 U.S.C. § 112, first paragraph, obviated, it would properly benefit from the filing date of Application No. 10/229,345.

Therefore, at present, the effective filing date of claims 75, 84-91, 93-102, 104-106, 123,and 124 is deemed the filing date of the instant application, namely August 26, 2003.

Grounds of Objection and Rejection Withdrawn

8. Applicant's amendment and/or arguments filed August 21, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed December 19, 2006.

New Grounds of Objection and Rejection Maintained

Claim Objections

9. Claim 99 is objected for the following reason:

Claim 99 depends from claim 97, which in turn depends from claim 75. According to claim 97, the method of claim 75 further comprises determining the amount of said at least one secreted ColoUp2 polypeptide in the biological sample, where according to claim 75 is sample is obtained from a subject. For this reason, the

recitation of step (a): "determining the amount of said at least one secreted ColoUp2 polypeptide in the biological sample from said subject" in claim 99 is redundant.

It is suggested that this issue be remedied by amending claim 99 as follows:

> The method of claim 97, wherein the method further comprises: ~~(a) determining the amount of said at least one secreted ColoUp2 polypeptide in the biological sample from said subject; and (b)~~ comparing the amount ~~from step (a)~~ of said at least one secreted ColoUp2 polypeptide to an amount determined in a sample obtained from said subject in the past.

Appropriate correction or rebuttal is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 75, 84-91, 93-102, and 104-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75, 84-91, 93-102, and 104-106 are indefinite for the following reason:

Claim 75 is directed to a polypeptide produced by the expression of the nucleic acid having the nucleic acid sequence of SEQ ID NO: 5; however, the limitation "the nucleic acid" lacks proper antecedent basis; and because there are a plurality of nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO: 5, it cannot be determined to which one nucleic acid the claim refers. Accordingly, the claims fail to delineate the subject matter that is regarded as the invention with the clarity and particularity necessary to permit the skilled artisan to know or determine infringing subject matter, so as to thereby satisfy the requirement set forth under 35 U.S.C. § 112, first paragraph[2].

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[2] Claims 123 and 124 are not rejected herein because the claims are directed to polypeptides comprising the amino acid sequences of SEQ ID NO: 21 and SEQ ID NO: 3, respectively; as such, the particular identify of the nucleic acid encoding the polypeptide is unnecessarily known in determining infringing subject matter.

It is suggested that it would be remedial to amend claim 75 to recite, for example, "a secreted polypeptide produced by the expression of a nucleic acid having the nucleotide sequence of SEQ ID NO: 5".

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 75, 84-91, 93-102, 104-106, 123, and 124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

(a) Claims 75, 84-91, 93-102, 104-106, 123, and 124 are directed to a genus of secreted polypeptides that are produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5.

According to claim 124, the polypeptide is a polypeptide comprising the amino acid sequence of SEQ ID NO: 3. SEQ ID NO: 3 is described as the amino acid sequence of the mature, secreted form of a polypeptide, which is present in the serum of subjects afflicted by colon cancer; see, e.g., Figure 2; and paragraphs [0126] and

[0127] of the published application[3]. Although present in the media of transfected cells expressing a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5[4], since the specification only establishes that the gene encoding the polypeptide of SEQ ID NO: 14 is overexpressed in colon cancer and adenomas by an analysis of mRNA levels[5], it is aptly noted that the presence of the polypeptide of SEQ ID NO: 3 in the serum or other bodily fluid obtained from a subject has not been correlated with the presence in the subject of a colon neoplasm.

The, according to claim 123, the polypeptide that is produced by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 is a polypeptide comprising the amino acid sequence of SEQ ID NO: 21. SEQ ID NO: 21 appears to be but a mere fragment of the amino acid sequence of the mature, secreted polypeptide (i.e., SEQ ID NO: 3)[6]. However, the specification incongruously discloses that the polypeptide of SEQ ID NO: 21 is structurally distinct from the polypeptide of SEQ ID NO: 3: "A peptide of sequence AVLAAHCPFYSWK was present only in the digest of the 55 KD fragment, but was absent from the digest of the full length protein, demonstrating that this peptide corresponded to the unique amino terminus of the 55 KD fragment" (paragraph [0180] of the published application)[7]. Although present in the media of transfected cells expressing a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5[8], it is again noted that the specification only establishes that the gene is overexpressed in colon cancer and adenomas by an analysis of mRNA levels; therefore, the presence of the polypeptide of SEQ ID NO: 21 in the serum or other bodily fluid obtained from a subject has not been correlated with the presence in the subject of a colon neoplasm. Nonetheless, because of the disclosed structural differences between the polypeptide of SEQ ID NO: 3 and the polypeptide of SEQ ID

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[3] U.S. Patent Application No. 2006/0035237 A1.
[4] See, e.g., paragraphs [0178] and [180] of the published application.
[5] See, e.g., paragraphs [0159] and [0167].
[6] SEQ ID NO: 21 consists of the amino acid sequence set forth between the amino acids at positions 245-732, inclusive, of SEQ ID NO: 3.
[7] This disclosure suggests the amino acid sequence of the disclosed 55 kDa polypeptide cannot be the amino acid sequence set forth as SEQ ID NO: 21.
[8] See, e.g., paragraphs [0178] and [180] of the published application.

NO: 21, there is a reasonable presumption that the polypeptides have different activities and/or biologic functions.

Apart from the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, the specification also describes another polypeptide, which is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, namely the polypeptide of SEQ ID NO: 14. The polypeptide of SEQ ID NO: 14, however, is the full-length polypeptide, which is processed to yield the mature polypeptide of SEQ ID NO: 3. The polypeptide of SEQ ID NO: 14 is not secreted.

Otherwise, if not a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and/or SEQ ID NO: 21, the specification fails to describe with any of the requisite degree of clarity and particularity the structures of the secreted "ColoUp2" polypeptides that encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5.

Notably, the specification defines the term "ColoUpX" (e.g., ColoUp2) as "a nucleic acid encoding a ColoUp protein or a ColoUp protein itself, as well as distinguishable fragments of such nucleic acids and proteins, longer nucleic acids and polypeptides that comprise distinguishable fragments or full length nucleic acids or polypeptides, and variants thereof" (paragraph [0078] of the published application). It continues, disclosing that said "[v]ariants include polypeptides that are at least 90% identical to the relevant human ColoUp SEQ ID Nos. referred to in the application, and nucleic acids encoding such variant polypeptides" (paragraph [0078] of the published application); and moreover, said variants include "different post-translational modifications, such as glycosylations, methylations, etc." (paragraph [0078] of the published application). The specification discloses that "[p]articularly preferred variants include any naturally occurring variants, such as allelic differences, mutations that occur in a neoplasia and secreted or processed forms" (paragraph [0078] of the published application).

Then, at paragraph [0025] of the published application, the specification further describes the term "ColoUp2" with the following disclosure:

> [A] secreted ColoUp2 polypeptide is selected from among: a) a secreted polypeptide produced by the expression of a nucleic acid that is at least 95% identical to the amino acid sequence of SEQ ID No: 5; b) a secreted polypeptide produced by the expression of a nucleic acid that is a naturally occurring variant of SEQ ID No: 5; c) a secreted polypeptide produced by the expression of a nucleic acid that hybridizes under stringent conditions to a nucleic acid sequence of SEQ ID No: 5; d) a secreted polypeptide having a sequence that is at least 95% identical to the amino acid sequence of SEQ ID No: 3; and e) a secreted polypeptide having a sequence that is at least 95% identical to the amino acid sequence of SEQ ID No: 21. Optionally, the secreted ColoUp2 polypeptide is produced by the expression of a nucleic acid having the sequence of SEQ ID No: 5, and preferably the secreted ColoUp2 polypeptide is produced by the expression of a nucleic acid sequence that is at least 98%, 99% or 100% identical to the nucleic acid sequence of SEQ ID No: 5. In certain embodiments, the secreted ColoUp2 polypeptide has an amino acid sequence that is at least 98%, 99% or 100% identical to an amino acid sequence selected from among SEQ ID No: 3 and SEQ ID No:21.

Accordingly, though the claims are directed to a genus of secreted "ColoUp2" polypeptides that are produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, this genus includes structurally disparate polypeptides, such as any naturally occurring variants of the polypeptide of SEQ ID NO: 2, which differ therefrom by allelic differences and/or mutations that occur during oncogenesis, as well has secreted and processed isoforms thereof[9].

Notably, neither the specific activities and/or biological functions of the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, nor of any other secreted "ColoUp2" polypeptide that is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, have been described in the specification.

As such, the claims are directed to a genus of polypeptides having structures that vary, albeit to a finite extent, and which differ substantially in function and/or specific activity.

Though the specification describes the polypeptide of SEQ ID NO: 3 and SEQ ID NO: 21 as a member of the genus of secreted "ColoUp2" polypeptides to which the claims are directed, it is submitted that neither polypeptide is reasonably deemed representative of the genus, as a whole. Absent a disclosure of at least one particularly identifying structural feature that is shared by the polypeptide of SEQ ID NO: 3 and at

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[9] Given the disclosed structural differences between the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, both of which are supposedly encoded by the same nucleic acid (i.e., a nucleic acid comprising the

least a substantial number of the other members of the genus of polypeptides to which the claims are directed, which correlates with any one common functional attribute of at least most of these polypeptides, the skilled artisan could not immediately envision, recognize or distinguish the polypeptides that are detected in the biological sample, so as to provide an indication that the subject is likely to have a colon neoplasm. As such, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

There is a reasonable presumption that the amino acid sequences of at least some of the plurality of polypeptides that might be produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 differ substantially from that of the disclosed mature, secreted polypeptide of SEQ ID NO: 3. As a consequence of such structural variation, it is expected that a number of the polypeptides to which the claims are directed will not have or retain the specific activities and/or biologic functions of the polypeptide of SEQ ID NO: 3. This position is supported, for example, by the teachings of Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39) (of record; cited by Applicant). Skolnick et al. discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a variant of the polypeptide of SEQ ID NO: 3 is capable of functioning the same, or even as having the same structure as the polypeptide of SEQ ID NO: 3.

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nucleotide sequence of SEQ ID NO: 5), it appears that these polypeptides are perhaps the translation products of alternatively spliced mRNA molecules.

Notably, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

In addition, while some of members of the genus of polypeptides to which the claims are directed may not have or retain the specific activities of the polypeptide of SEQ ID NO: 3, it is further noted that at least some of the polypeptides to which the claims are directed would not be reasonably expected to be secreted into the serum or other biological fluids of subjects afflicted with colon cancer; as such, the presence of some of the polypeptides that might be produced by expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 may not be indicative of the presence in the subject of a colon tumor.

Even among closely related protein family members, the skilled artisan cannot predict whether a particular member of the family is associated with the etiology or pathology a specific disease, solely on the basis that another member of the family has been shown to be. De Plaen et al. (*Immunogenetics*. 1994; **40**: 360-369) (of record; cited by Applicant), for example, reviews the structure, chromosomal localization and expression of twelve genes encoding members of the MAGE family of proteins; see entire document (e.g., the abstract). De Plaen et al. teaches six of the members of the gene family were found to be expressed at a high level in a number of tumors of various histological types; while five were very weakly expressed in all samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (page 367, column 1). Just as not all members of the MAGE family of proteins are associated with cancer, particularly, since is it not obvious what, if any, association the weakly expressed MAGE proteins have, it is apparent that the skilled artisan cannot predict, based upon the information disclosed in the specification, whether variants of the polypeptide of SEQ ID NO: 3, as members of a presumed family of structurally

related proteins, have an association with the etiology or pathology of colon cancer (e.g., whether the genes encoding such variants are overexpressed in colon cancer).

For this reason, Applicant is reminded: "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, as in that, there is no language that adequately describes with the requisite clarity and particularity the genus of structurally and functionally disparate polypeptides to which the claims are directed, the presence of which in a biological sample obtained from a subject is indicative of the presence in the subject of a colon neoplasm. A description of how a material may be used, rather than of what it is, does not suffice to describe the claimed invention.

Although the skilled artisan could potentially determine whether the presence in a biological sample acquired from a subject of any given member of a genus of polypeptides encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 is indicative of colon cancer or adenoma in the subject, M.P.E.P. § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CA FC 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CA FC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CA FC 1991).

Finally, "Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

(b) With further particular regard to claims 123 and 124, which are directed to the method of claim 75, wherein the secreted "ColoUp2" polypeptide is a polypeptide comprising the amino acid sequences of SEQ ID NO: 21 and SEQ ID NO: 3, respectively:

As explained above, the polypeptide of SEQ ID NO: 3 is allegedly a mature, secreted isoform of the full-length polypeptide of SEQ ID NO: 14, which is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5; see, e.g., paragraph [0032] of the published application; and Figure 2. The polypeptide of SEQ ID NO: 21 comprises an amino acid sequence comprising a fragment of the amino acid

sequence of SEQ ID NO: 3, but still differs from the polypeptide of SEQ ID NO: 3 by the inclusion in its amino acid sequence of a novel amino acid sequence; see, e.g., paragraph [0180] of the published application; and Figure 41.

As disclosed in the specification, molecular markers that occur in the urine are generally derived from a polypeptide that is present in the blood (paragraph [0099] of the published application); therefore, if the "ColoUp2" polypeptide is not secreted, it is not likely to be present in the blood or any fraction thereof. Notably, the specification further discloses that a molecular marker that is present in the lumen of the colon may be found in the intestinal mucous or in stool samples), provided the marker is secreted from the apical face of a cell (paragraph [0099] of the published application). So, if the "ColoUp2" polypeptide is not secreted from the apical face of the colon cell into the lumen, it may not be present in, for example, the stool of a subject. The skilled artisan cannot predict whether any given variant of the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 is indicative of the presence in the subject of any precancerous or cancerous condition or disease in a subject, the skilled artisan also cannot predict whether such variants are secreted and/or present in the blood, urine, or stool of subjects having or likely to have a colon neoplasm. Moreover, while many of "ColoUp2" polypeptides may not be secreted, it is also expected that colon cells, as well as other types of cells, express and secrete at least some of the "ColoUp2" polypeptides, such that their presence alone in any given biological sample would not provide such an indication. As further explained in the following rejection of the claims, as failing to provide a sufficiently enabling disclosure to satisfy the requirement set forth under 35 U.S.C. § 112, first paragraph, this is indeed the case, since WO 2002/86443 A2, for example, teaches a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 is secreted into the serum and other biological fluids by lung cancer cells; see entire document (e.g., pages 351 and 352). Similarly, WO 2002/102235 A2 teaches ovarian cancer cells secrete this same polypeptide; see entire document (e.g., pages 304 and 305).

Therefore, it is noted that the specification discloses that Applicant predicts that "ColoUp2" is likely secreted at least in part from the basolateral epithelial face, and

hence should be detectable as a serologic marker of large colon adenomas; see paragraphs [0169] and [0178] of the published application). Yet, while perhaps the presence of secreted isoforms of the polypeptide of SEQ ID NO: 14 in the serum of subjects may ultimately be found to provide an indication that the subject has such large colon adenomas or adenocarcinomas, it is submitted that because of an evident lack of particularity the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Indeed, the specification describes the presence of a transcript encoding the polypeptide of SEQ ID NO: 14 in premalignant colon adenomas, as well as in 90% of Dukes stage B (early node negative colon cancers), Dukes stage C (node positive colon cancer), Dukes stage D (primary colon cancers with associated metastatic spread) and in colon cancer liver metastasis, colon cancer cell lines, and in colon cancer xenografts grown in athymic mice (paragraphs [0167] of the published application). However, the specification only shows that *transfected* cell lines, which have been engineered to express a nucleic acid molecule encoding the full-length polypeptide of SEQ ID NO: 14, secrete the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 (see, e.g., paragraph [0174], [0177], and [0178] of the published application); it fails to demonstrate the presence of either polypeptide in the blood, or a fraction thereof, urine, or stool of a subject known to have any precancerous or cancerous growth of the colon. Contrary to Applicant's assertion, the expression of the gene encoding the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 may not yield detectable quantities of the polypeptides in the blood, urine, or stool because the specification has not disclosed that the amount of the polypeptide secreted by the cells is concordant with the amount of mRNA produced by the cell. It is well established one cannot predict whether the level of protein produced by a cell will reflect the amount of mRNA produced by the cell: "But having acknowledged that control of gene expression can occur at multiple stages, *and that production of RNA cannot inevitably be equated with production of protein*, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription" (italicized for emphasis) (Genes VI, 1997; Ed. Benjamin Lewin; Chapter 29, first page). As further emphasized by the teachings of Chen et al. (*Molecular &*

Cellular Proteomics. 2002; **1**: 304-313) (of record; cited by Applicant), one cannot merely presume that, because there is an association between the amount of mRNA produced by a given sample of cells and the presence of cancer, the amount of protein encoded by that mRNA may also associated with the presence of cancer in the sample. Chen et al. teaches expression of protein and mRNA in cancer are discordant; see entire document (e.g., the abstract). Liu et al. (*Cancer J.* 2001 Sep-Oct; **7** (5): 395-403) (of record; cited by Applicant) shows similarly that the amplification of the gene encoding HER-2, another tumor-associated antigen, which often leads to over-expression, does not necessarily correlate with over-expression. Liu et al. shows that amplification of the gene encoding HER-2 was detected in a substantial portion of prostate cancer cells that do not over-express the protein; see entire document (e.g., the abstract). Given such facts, it is submitted that a demonstration that transfected xenografts artificially secreted detectable quantities of the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 into the sera of mice, such as that presented in this application (paragraph [0174] of the published application) should not suffice to establish the presence of either polypeptide in a subject having or likely to have a colon neoplasm, such as a polyp, adenoma, or adenocarcinoma. Such a demonstration does not determine whether the amount of the polypeptide secreted into the blood, urine, or stool by the cells of such colon neoplasms in human subjects, for example, is concordant with the amount of mRNA produced by those cells.

Support for this position is found, for example, in the teachings of Roessler et al. (*Mol. Cell. Prot.* 2006; **5** (11): 2092-2101). Roessler et al. teaches that of five proteins identified as elevated in tissue samples obtained from individuals with colorectal cancer only one of these proteins could be shown to be elevated in serum samples obtained from individuals with colorectal cancer; see entire document (e.g., page 2099, right column). Additionally, Roessler et al. (*Clin. Can. Res.* 2005; **11** (18): 6550-6557) teaches, while proteins may be elevated in tissue samples obtained from individuals with colorectal cancer, "which of the cancer-associated proteins found in tumor tissue that eventually will be present in serum or plasma cannot be predicted *a priori*"; see entire document (e.g., page 6556, right column). Thus, according to Roessler et al.,

development of highly sensitive immunoassays for each candidate marker and subsequent assessment of serum/plasma samples is mandatory (page 6556, right column). Similarly, Zolg et al. (*Mol. Cell. Prot.* 2004; **3** (4): 345-354) discloses, upon commenting on whether proteins identified as elevated in cancer tissue screens will also be elevated in liquid samples obtained from individuals, "[an] inherent risk in the tissue approach is the fact that the candidate marker identified in e.g., tissue cannot later be detected in peripheral fluid such [as] serum"; see entire document (e.g. page 347, right column).

14. Claims 75, 84-91, 93-102, 104-106, 123, and 124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3, **does not reasonably provide enablement for using** the claimed processes for determining whether a subject is likely to have a colon neoplasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*,

858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the "written description" rejection above, the claims are directed to a genus of secreted "ColoUp2" polypeptides, which are encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, but which differ both structurally and functionally. As further explained above, the skilled artisan cannot predict, based upon the information disclosed in the specification, whether secreted "variants" of the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, which most broadly include any polypeptide that might be produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, even as members of a presumed family of structurally related proteins, have an association with the etiology or pathology of colon precancer and colon cancer. That is, for example, the skilled artisan cannot predict whether the genes encoding such secreted variants are overexpressed in colonic polyps, adenomas, or colon cancer, as compared to normal colon tissue, or whether the polypeptides encoded by these gene are secreted into the blood, urine, or stool of a subject afflicted by the condition or disease, so as to serve as biomarkers of the disease.

The specification describes that the presence of a secreted polypeptide(s) having the amino acid sequences of SEQ ID NO: 3 or SEQ ID NO: 21 in the conditioned medium used to culture transfected cells expressing nucleic acid molecules encoding these proteins; see, e.g., paragraph [0171] of the published application. Similarly, the

specification describes the appearance of these polypeptide(s) in the serum of mice implanted with transfected xenograft tumor cells expressing the polypeptide(s); see, e.g., paragraph [0174] of the published application.

The specification, however, fails to demonstrate the presence of any one of the "ColoUp2" polypeptides (e.g., the polypeptide of SEQ ID NO: 3) in any biological sample, such as blood, urine, or stool acquired from subjects known to have a colonic polyp, a colon adenoma or a colon carcinoma; moreover, apart from the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, it appears that the disclosure fails to describe with the requisite particularity any other "ColoUp2" polypeptide that is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, which may serve as a plasma, serum, urine, or stool marker, for example, of such colon neoplasms.

Again, considering the vastly different structures and functions of the members of the genus of polypeptides to which claims are directed, it is reasonably expected that the presence in a biological sample of most of the polypeptides to which the claims are specifically directed would not provide an indication of the presence of such a condition or disease, or of the likelihood that the subject has such a condition or disease, since, for example, many of the polypeptides may not be expressed in the normal colon or even in colon cancer cells. Thus, any success in practicing of the claimed invention by determining the presence of any polypeptide other than the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 is most unpredictable, but because the specification fails to establish the presence of the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 in the blood, urine or stool of a subject having or likely to have a colonic polyp, adenoma, or carcinoma, it is submitted that the skilled artisan could not practice any one embodiment of the claimed invention without undue and/or unreasonable experimentation. Before the skilled artisan might reasonably be capable of using the claimed process to achieve the claimed objective (i.e., the determination that a subject has or is likely to have a colon neoplasm), it would be necessary to determine if the "ColoUp2" polypeptide (e.g., the polypeptide of SEQ ID NO: 3) is actually secreted into the blood of a subject known to have such a colon neoplasm, and then whether or not its presence in the blood, urine, or stool of the subject is indicative of the presence in

the subject of the colon neoplasm, as opposed to, for example, the presence of some other normal or abnormal cell type that also expresses the polypeptide. Even then, it would still be necessary to identify other secreted polypeptides that are produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 (e.g., other isoforms encoded by splice variants of the mRNA encoding the polypeptides of SEQ ID NO: 14, SEQ ID NO: 3 and/or SEQ ID NO: 21), which are suitable markers for colon neoplasms, and then it would be necessary to elaborate the processes for detecting the presence of such neoplasms in a biological sample that involves the detection of those other polypeptides.

Given, in particular, the degree to which the members of the "ColoUp2" polypeptides may vary, both structurally and functionally, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a secreted "ColoUp2" polypeptide present in a biological sample of a subject having or likely to have a colon neoplasm, which might serve as a biomarker of that condition or disease.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

The molecular detection and diagnosis of cancer, or the molecular assessment of a subject's risk for (i.e., the likelihood of) developing cancer is a highly unpredictable art, because of the complexities of the biological systems and the many and variable mechanisms by which cancer forms and progresses. In the absence of scientific and clinical validation of the utility of a putative biomarker, such as the polypeptide of SEQ ID NO: 3, the skilled artisan could not use the claimed invention to detect the presence

of a precancerous or cancerous neoplasm of the colon, or to assess a subject's risk for developing such a condition or disease.

The teachings of Rae et al. (*International Journal of Cancer.* 2000; **88**: 726-732), for example, emphasizes the need to validate initial studies suggesting that a gene encoding a tumor marker is overexpressed in carefully controlled studies using "matched" (i.e., acquired from the same subject) normal control specimens. Rae et al. teaches a highly sensitive method for determining the differential expression of genes associated with cancer; see entire document (e.g., the abstract). A total of sixteen tumor and sixteen adjacent normal tissue samples were collected at the same time from the patients. The tumor tissue was histologically confirmed to be clear-cell renal cell carcinoma (RCC); and the tumors were staged by a conventional system. Rae et al. discloses that using differential display PCR, it was determined that some genes were identified that were expressed at higher levels in the tumor specimens than in the normal specimens, while other genes were expressed at lower levels in the tumor specimens. Notably, Rae et al. had planned to use as a positive control, primers that amplify a complementary DNA (cDNA) molecule encoding "DD96", a gene that had been previously reported by Kocher et al. to be up regulated in RCC. However, Rae et al. found that in contrast to the results reported by Kocher, et al, no *consistent* up- or down-regulation of *DD96* was evident when using either RT-PCR or Northern analysis. Rae et al. concludes, "we do not believe that *DD96* up-regulation is highly associated with RCC, particularly in early progression, and does not warrant extensive further investigation in the context of this disease" (page 731, column 2). Rae et al. suggests that the results of Kocher et al. were inaccurate because their experiments were not properly controlled. In contrast to the study of Kocher et al., Rae et al. discloses, "only those cDNAs clearly up- or down-regulated in duplicate paired RCC and normal kidney samples (Fig. 1) from 4 different patients were considered to be definitively differentially expressed" (page 728, column 1). Moreover, their results were considered accurate only when the cDNAs were successfully re-amplified and only when no expression was detected in the paired (i.e., matched) sample. Thus, while the specification may disclose data that is suggestive that a nucleic acid encoding the polypeptide of SEQ ID

NO: 14, and presumably the secreted isoforms thereof comprising the amino acid sequences of SEQ ID NO: 3 and/or SEQ ID NO: 21, is present in relatively greater abundance in colon adenoma cells and colon cancer cells, as compared to normal colon cells, because the data was not apparently acquired using appropriately matched controls as references, it is submitted that the results would have to be verified before it would be prudent to determine if the presence of the protein in any given biological sample acquired from a subject, such as blood or urine, is indicative of the presence in the subject of a colon neoplasm.

Notably, even in instances where carefully controlled experiments establish the that a biomarker is differentially expressed by cancer cells, compared to matched normal cells of the same tissue, the determination of the presence or expression of some tumor markers has proven to be ineffective in enabling an accurate and reliable diagnosis of all stages of cancer. Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis; see, e.g., pages 96 and 97. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease; see, e.g., pages 98 and 99.

Critchfield (*Disease Markers* 1999; **15**: 108-111) teaches: "Indeed, to truly benefit society, the clinical value of the gene must be established" (page 109, column 1). Following the discovery of a novel gene, Critchfield discloses the process of determining whether the gene can be used successfully as a biomarker for diagnosis is lengthy and involved. Similarly, the discovery of a possible association between the expression of a gene and cancer would be followed by an equally long and arduous process by which it is determined if the over- or under-expression of the gene in cancer cells, relative to its normal level of expression in normal cells, can be used to diagnose or detect cancer. Sidransky (*Science* 1997; **278**: 1054-1058) teaches this process must first establish the reliability of a novel diagnostic method, which measures the expression of a biomarker, through feasibility studies; then, after the reliability of the technique is established, its sensitivity and specificity must be assessed in formal

clinical trials before the technique can be used with a reasonable expectation of success (page 1055, columns 1 and 2). Tockman et al. (*Cancer Research* 1992; **52**: 2711s-2718s) teaches considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman et al. teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2).

In this instance, there is considerable evidence that the claimed process could not be used to achieve the claimed objective of determining whether a subject has or is likely to have a colon neoplasm, particularly if the biological sample is not of the colon, but is instead a sample of the subject's blood, urine, or stool. WO 2002/102235 A2 (Mack et al.) teaches a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 3; but Mack et al. teaches the polypeptide is overexpressed in ovarian cancer. Thus, the presence of the polypeptide

comprising the amino acid sequence of SEQ ID NO: 3 in the serum of a subject is not necessarily indicative of the presence in the subject of a colon neoplasm, since it is instead just as likely due to the presence in the subject of ovarian cancer. Similarly, WO 2002/86443 A2 (Aziz et al.) teaches a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 3; but Aziz et al. teaches the polypeptide is overexpressed in lung cancer. Thus, it is again apparent that the presence of the polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in the serum of a subject is not necessarily indicative of the presence in the subject of a colon neoplasm, but may instead just as likely be due to the presence in the subject of lung cancer, if not ovarian cancer.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 75, 84-87, 89-91, 93-98, 100-102, 104-106, 123, and 124 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2004/0005563 A1 (of record; cited by Applicant).

The claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

U.S. Patent Application Publication No. 2004/0005563 A1 (Mack et al.) teaches a process comprising obtaining a biological sample from a subject and detecting in the biological sample the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 87, which is identical to the amino acid sequence of SEQ ID NO: 3, as disclosed in this application, and comprises the amino acid sequence of SEQ ID NO: 21, also as disclosed in this application; see entire document (e.g., paragraphs [0213], [0216], [0217], [0220], [0222], and [0241]). Mack et al. teaches the biological sample obtained from the individual is a sample of blood or a fraction thereof (i.e., plasma or serum), or stool; see, e.g., paragraphs [0061], [0140], and [0220]. Mack et al. teaches the presence and/or amount the polypeptide in the biological sample is determined by an immunoassay that employs an antibody that binds to the polypeptide, such as immunoprecipitations, Western blot analyses, and/or ELISAs; see, e.g., paragraphs [0220] and [0264]. Accordingly, Mack et al. teaches the antibody is detectably labeled with a detectable substance, such as an enzyme, fluorescent substance, chemiluminescent substance, a chromophore, a radioactive isotope, or a complexing agent (e.g., a detectably labeled secondary antibody); see, e.g., paragraphs [0218]-[0220] and [0264]. Mack et al. teaches the process comprises determining the amount of the polypeptide in a biological sample obtained from a normal subject and comparing the values of the amounts of the polypeptides in the different samples; see, e.g., paragraphs [0041], [0111], and [0349]. Mack et al. teaches the process aids in determining therapeutic protocols; see, e.g., paragraphs [0105] and [0106].

In addition, Mack et al. does not teach that the subject is previously diagnosed with any disease, such as cancer; so, it follows that the process disclosed by Mack et al. is practiced using a subject according to claim 102, namely a subject not previously diagnosed with colon cancer.

17. Claims 75, 84, 85-87, 89-91, 93-98, 100-102, 104-106, 123, and 124 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 2002/068677 A1 (of record; cited by Applicant).

The claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

WO 2002/268677 A1 (Mack et al.) teaches a secreted polypeptide comprising an amino acid sequence that is identical to the amino acid sequence of SEQ ID NO: 3 and which comprises the amino acid sequence of SEQ ID NO: 21; see entire document (e.g., page 249, SEQ ID NO: 23; and Table 25 at page 238; and Table 21 at page 221). Mack et al. teaches the gene encoding this polypeptide is up-regulated in colon cancer, as compared to its level of expression in normal colon tissue; see, e.g., Table 21 at page 221. Mack et al. teaches detecting colon cancer in a subject by acquiring a biological sample (e.g., a sample of blood, serum, or stool) and determining if the secreted polypeptide is present in the sample using an immunoassay that employs a labeled or unlabeled antibody that binds to the polypeptide; see, e.g., pages 3, 5, 22, 23, 32, 33, 45-50, 52 and 53. Mack et al. teaches the process comprises quantifying the level of expression by measuring the amount of the polypeptide in the sample; see, e.g., page 51. Mack et al. teaches the immunoassay is an assay involving a Western blot, an immunoprecipitation assay, a radioimmunoassay, or an ELISA; see, e.g., page 53. Mack et al. teaches the antibody that is used in such assays, when labeled, is labeled using an enzyme, radioactive moiety, chromophore, or fluorescent or chemiluminescent substance; see, e.g., pages 15, 16, and 53. Mack et al. teaches the subject has either not been previously diagnosed or is currently receiving therapy for

colon cancer; see, e.g.; page 3. Mack et al. teaches the process detects metastatic colon cancer, as well as precancerous or benign conditions, such as colon adenoma; see, e.g., pages 5 and 8. Mack et al. teaches the process comprises determining the amount of the polypeptide in a biological sample obtained from a normal subject and comparing the values of the amounts of the polypeptides in the different samples; see, e.g., Table 21 at page 221. Mack et al. teaches the detection of the presence of the polypeptide in a biological sample aids in the determining the therapeutic protocol to be administered to a subject having colon cancer; see, e.g., pages 2-8.

18. Claims 75, 84-87, 89-91, 93-102, 104-106, 123, and 124 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 2002/86443 A2.

The claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

WO 2002/86443 A2 (Aziz et al.) teaches a process comprising obtaining a biological sample from a subject and detecting in the biological sample the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 87, which is identical to the amino acid sequence of SEQ ID NO: 3, as disclosed in this application, and comprises the amino acid sequence of SEQ ID NO: 21, also as disclosed in this application; see entire document (e.g., page 5, lines 31-33; page 8, lines 9-19; page 34, lines 7-9; pages 351 and 352, SEQ ID NOs: 444 and 445). Aziz et al. teaches the biological sample obtained from the individual is a sample of blood or a fraction thereof (i.e., plasma or serum), or stool; see, e.g., page 9, lines 15-25. Aziz et al. teaches the presence and/or amount the polypeptide in the biological sample is determined by an immunoassay that employs an antibody that binds to the polypeptide, such as immunoprecipitations, Western blot analyses, and/or ELISAs; see, e.g., page 49, lines 26 and 27; and page 53, line 14, through page 54, line 20. Accordingly, Mack et al. teaches the antibody is detectably labeled with a detectable substance, such as an enzyme, fluorescent substance, chemiluminescent substance, a chromophore, a

radioactive isotope, or a complexing agent (e.g., a detectably labeled secondary antibody); see, e.g., page 16, lines 11-21. Aziz et al. teaches the process comprises determining the amount of the polypeptide in a biological sample obtained from a normal subject and comparing the values of the amounts of the polypeptides in the different samples; see, e.g., page 4, lines 28-31; and Tables 1-16, beginning at page 83. Aziz et al. teaches the comparison is made using the values of the amounts of the polypeptide in sample acquired at multiple time points (e.g., using a sample obtained from the patient in past, as well as the present); see, page 4, lines 28-31; and page 9, lines 26-31. Aziz et al. teaches the process aids in determining therapeutic protocols; see, e.g., page 54, line 24, through page 55, line 4.

In addition, Aziz et al. does not teach that the subject is previously diagnosed with any disease, such as cancer; so, it follows that the process disclosed by Aziz et al. is practiced using a subject according to claim 102, namely a subject not previously diagnosed with colon cancer.

Conclusion

19. No claim is allowed.

20. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. WO 2002/30268 A2 (Gish et al.) (of record; cited by Applicant) teaches a secreted polypeptide comprising an amino acid sequence that is nearly identical to SEQ ID NO: 3, which is present in the serum of patients afflicted by prostate cancer.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

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